REMARKS

Claims 1-20 remain in this application. The specification and claims 1-11 and 13-20 are amended. Support for the amendments can be found in the specification and original claims as filed. No new matter has been added.

OBJECTIONS TO THE SPECIFICATION

Trademarks

The Office Action requests that the Trademarks be capitalized and accompanied by generic terminology. Applicants have amended the specification to address this issue.

Minor Informalities

The Office Action objects to the specification because of minor informalities. Applicants have amended the specification to address each of the informalities.

1. The term "arthrotic" has been replaced by "arthritic" at page 1 of the specification.

2. The term "remainance" has been replaced by "persistence" throughout the specification.

3. The term "microphages" has been replaced by "macrophages" throughout the specification.

4. The phrase "viscoelastic gel comprised by a matrix..." has been replaced by "viscoelastic gel comprised of a matrix..." at page 4 of the specification.

5. The terms "chondroitine" and "carraghenin" have been replaced by correctly spelled "chondroitin" and "carrageenan", respectively, throughout the specification.

Accordingly, Applicants request reconsideration and withdrawal of the objection to the specification.

CLAIM OBJECTIONS

Duplicate Claims

The Office Action objects to claim 17 as being a substantial duplicate of claim 15. Amended claim 17 now depends from claim 4; claim 15 depends from claim 2. Thus, the scope of claims 15 and 17 are different and the claims are not substantial duplicates.

Minor Informalities

The Office Action objects to claims 7 and 8 because of informalities, specifically, the misspelling of the terms "chondroitine" and "carraghenin". Amended claims 7 and 8 correct the misspelled terms.

Accordingly, Applicants request reconsideration and withdrawal of the claim objections.

CLAIM REJECTION - 35 USC § 102

At page 3, the Office Action rejects claims 1-4, 6, 9-10, 12-14 and 18-20 under 35 U.S.C. § 102(b) as being

anticipated by BERG et al. (US 6,165,489). Applicants respectfully traverse the rejection.

Claim 1 is directed to a process for the production of a biocompatible crosslinked gel. Claims 2-4, 6, 9, 13-14 and 18-20 depend from claim 1. Claim 10 is directed to a gel prepared by the process of claim 1 and claim 12 is directed the use of the gel of claim 10 and so claims 10 and 12 are also closely related to the process of claim 1. BERG fails to teach or suggest such a process.

BERG describes a collagen composition that includes particulate crosslinked collagen and a chemical crosslinking agent. The term "particulate crosslinked collagen" is defined as "an aqueous dispersion of insoluble crosslinked collagen particles" (*see*, column 3, lines 7-9). This particulate crosslinked collagen is mixed with noncrosslinked collagen in an amount of 25 to 95 percent by weight of the final composition. The composition to be injected thus contains particles of crosslinked collagen dispersed in noncrosslinked collagen and is heterogeneous.

As detailed in the instant specification, the BERG composition is obviously biphasic, because it corresponds exactly to the two descriptions: it is comprised of a matrix dispersed in a liquid phase, and it is constituted by a fluid phase (non-crosslinked) and a highly crosslinked phase (*see*, page 4, lines 8-24).

On the contrary, a main feature of the crosslinked gel to be injected according to the present application is that it is monophasic, i.e. homogeneous with only one single visible phase. Any composition that includes particles dispersed in a liquid phase (aqueous) or in a fluid phase (non-crosslinked) cannot be considered as monophasic. According to the presently claimed process for the production of a biocompatible crosslinked gel, the crosslinking of the biocompatible polymer is effected in two steps: a first crosslinking step of the polymer during which strongly crosslinked hubs are formed, and a second crosslinking step during which a less and less crosslinked gel is formed, the whole gel remaining continuous (*see*, page 11 of the present specification and claim 1). The formation of the less and less crosslinked gel is due to the decrease in the crosslinking agent content which has already partly been used in the first step and to the dilution of the solution.

The change from a heterogeneous composition to a homogeneous one is important because, as mentioned in the present specification, it is known that the presence of particles or residual fragments in biphasic compositions results in secondary reactions such as an inflammatory reaction or granulomas (see, page 2, lines 28-32, and page 4, lines 28-31).

After the crosslinking steps, the crosslinking agent is removed, preferably by dialysis. The gel to be injected no longer contains significant amount of a crosslinking agent. It is also

not intended to have crosslinking taking place after injection of the gel into the patient.

In contrast to the presently claimed method, in BERG, the composition to be injected contains collagen particles and a significant amount of crosslinking agent. The crosslinking reaction is intended to take place *in situ* to anchor the collagen implant to host tissue. Collagen particles are thus present in host tissue and will result in secondary reactions as explained above. In distinction from BERG, the presently claimed process results in a composition that does not include crosslinking agent as it has substantially been removed, for example, by dialysis.

In addition, the structure of the gel obtained in the presently claimed process includes strongly crosslinked hubs and a less and less crosslinked gel interconnected with the hubs, the whole gel remaining continuous. BERG fails to teach or suggest this specific structure. The gel structure is obtained by a specific and accurate process that includes:

- crosslinking of a biocompatible polymer;
- in the resulting reaction mixture, adding a supplemental amount of polymer with a specific Mw <u>with dilution</u> of the mixture, resulting in a further crosslinking step at a density lower than that obtained in the initial crosslinking; and
- stopping the crosslinking reaction <u>by removal of the crosslinking agent</u>.

BERG fails to teach or suggest any process that includes the steps of dilution or removal of the crosslinking agent.

The claimed process thus provides injectable compositions having surprisingly improved features as an easily injectable gel, a high stability of the gel structure resulting namely in stability of strength needed to inject the gel between its preparation time and the injection time. This is distinct from BERG in which the gel remains reactive before and after its injection to allow *in vivo* crosslinking. In BERG, the reactivity of the gel implies a modification of the injection strength in the course of time and, as shown in column 14, lines 22-25 of BERG, such a modification results in a gel that is difficult if not impossible to be injected.

For all of these reasons, BERG fails to teach or suggest, and fails to anticipate, a process for the production of a biocompatible crosslinked gel having the combination of features recited in claim 1, and claims 2-4, 6, 9, 13-14 and 18-20 dependant thereon, the gel of claim 10 and the use of the gel of claim 12. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CLAIM REJECTION - 35 USC § 103

At page 6, the Office Action rejects claims 5, 7-8, 11, and 15-17 under 35 U.S.C. § 103(a) as being obvious over BERG, in view of LAMBERTI et al. (US 2003/0232198 A1), ZHAO et al. (US

2002/0049281 A1), and HUBBELL et al. (US 6,060,582). Applicants respectfully traverse the rejection.

Claims 5, 7-8 and 15-17 depend from claim 1, and claim 11 depends from claim 10. As detailed in the above remarks, BERG fails to teach or suggest the process of claim 1 and the gel of claim 10. Thus, BERG fails to teach or suggest claims 5, 7-8, 11 and 15-17.

Furthermore, LAMBERTI, ZHAO and/or HUBBELL, alone or in combination, fail to remedy the deficiencies of BERG. In particular, these references fail to teach or suggest adding a supplemental amount of polymer with a specific Mw with dilution of the mixture, resulting in a further crosslinking step at a density lower than that obtained in the initial crosslinking, and stopping the crosslinking reaction by removal of the crosslinking agent, as featured in the process of claim 1. For at least these reasons, BERG, LAMBERTI, ZHAO and/or HUBBELL fail to teach or suggest, and would not have rendered obvious, claims 5, 7-8, 11, and 15-17. Thus, Applicants request reconsideration and withdrawal of the rejection.

SUBSTITUTE SPECIFICATION – 37 1.125(b)

There is submitted herewith a clean version of the substitute specification, as well as a copy with markings showing all the changes relative to the originally filed version, in accordance with 37 CFR 1.125(c). As was pointed out above, the

undersigned registered U.S. Patent attorney states pursuant to 37 1.125(b), that the substitute specification includes no new matter.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item(s):

☒ - a Substitute Specification and a marked-up copy of the originally-filed specification